American Journal of Epidemiology

Vol. 148, No. 5
Printed in U.S.A.

Population Attributable Risk of Renal Cell Cancer in Minnesota

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A population-based case-control study of renal cell cancer was conducted in Minnesota between 1988 and 1990. It included 690 histologically confirmed incident cases identified through the state cancer surveillance system, and 707 age and sex frequency-matched controls. In this paper, the authors present estimates of the proportion of renal cell cancer cases attributable (or population attributable risk (PAR)) to 1) well-established risk factors, namely smoking, excess weight, and hypertension, and 2) more speculative risk factors, namely elevated protein intake, history of renal disease (i.e., stone, injury, or infection) and high parity among women. These estimates were based on information obtained from directly interviewed subjects (65% of cases and 100% of controls). The PARs for the three main risk factors were 21% for hypertension (defined by a reported personal history of hypertension or of treatment with antihypertensive or diuretic drugs), 21% for excess weight (defined by an elevation of the usual body mass index above the first quartile), and 18% for smoking (past and current). Overall, these three factors accounted for 49% of cases. The proportion increased to 60% when the three more speculative risk factors were considered as well. Sex-specific analyses revealed a greater impact of smoking among men mainly due to a higher prevalence of past smoking. In contrast, the impact of hypertension and excess weight was greater among women due to higher relative risks. These results suggest that 1) intervention measures aimed at reducing smoking, excess weight, and hypertension could substantially lower the overall incidence of renal cell cancer, and 2) intervention measures may have to be sex-specific. Conversely, because at least 40% of cases remain unexplained by the risk factors under study, further etiologic research is needed into renal cell cancer, an increasingly common form of cancer. *Am J Epidemiol* 1998;148:424–30.

body mass index; case-control studies; dietary proteins; hypertension; kidney neoplasms; parity; smoking

Malignant tumors of the kidney are not uncommon. In the United States, such tumors rank about 10th in cancer incidence and mortality (1). It has been estimated that in 1998 29,900 new cases will be diagnosed and nearly 12,000 patients will die of renal cancer, most of which will be renal cell carcinoma (1). Moreover, since 1970, the age-adjusted incidence rates for renal cell cancer have increased about 2 percent per year in each of the four major race/sex groups in the United States (2). Incidence is generally higher in western countries than in Asia or Latin America, although rates are increasing in all areas of the world (3).

Received for publication June 17, 1996, and accepted for publication December 4, 1997.

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PAR, population attributable risk.

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We previously estimated relative risks of various factors for renal cell cancer in a population-based case-control study in Minnesota (4–8). In this paper, we present estimates of population attributable risk (PAR) for selected risk factors identified in this study population. The PAR is defined as the proportion of cases that can be related to a given risk factor (or set of risk factors) and is useful in assessing its impact at the population level. To our knowledge, this analysis constitutes the first attempt at a comprehensive population attributable risk study of the risk factors for renal cell cancer.

MATERIALS AND METHODS

Methods for this study have been described in detail elsewhere (4). Briefly, residents of Minnesota between ages 20 and 79 years, who were newly diagnosed with a histologically confirmed renal cell cancer (*International Classification of Diseases* 9th Revision (ICD-9) code 189.0) between July 1, 1988, and December 31, 1990, were identified through the state cancer surveil-

lance system (9). Of the 796 eligible cases, interviews were obtained for 690 (87 percent) including 241 interviews with next-of-kin of patients who died or were too ill to be interviewed.

Controls were sampled from residents in Minnesota, using a random digit dialing (RDD) method (10) for those under age 65 years and a systematic sampling of Health Care Financing Administration (HCFA) files (11) for those aged 65 years or older. The controls were frequency-matched to cases by sex and 5-year age groups. Overall interview response rate was 87 percent for HCFA controls and 84 percent for RDD controls (a product of a 93 percent response rate at the household-screening phase and a 90 percent response rate at the interview phase). A total of 707 controls were interviewed. Because virtually all of the cases and controls were white, we excluded from analysis the few nonwhite subjects.

In-person, structured interviews were conducted in the homes of the study subjects by trained interviewers to elicit information on demographic characteristics, lifetime use of tobacco and alcohol; reproductive history; history of height, weight, and selected medical conditions including hypertension; use of analgesics, prescription diuretics, and other anti-hypertensive drugs; and occupational history. To the extent possible, interviewers were blind with regard to the case-control status of subjects.

Body mass index (BMI) was computed for men (weight (kg)/ height $(m)^2$) and women (weight (kg)/ height $(m)^{1.5}$) (12), using the usual adult weight, highest adult weight, weight in each decade of life, and weight in the last decade (8). As regards reproductive history, information was sought on age at menarche and menopause, number of births and age at first birth, use of oral contraceptives and menopausal hormones, and history of hysterectomy and oophorectomy (6).

If a history of using diuretics or other antihypertensive drugs for at least twice a week for 2 weeks or longer was established, detailed information was collected on overall pattern of use, including age started and stopped, total duration, and usual dose taken. In addition, for personally interviewed cases and controls, detailed information was collected on the use of 13 specific diuretics and 22 other antihypertensive drugs. Ever use of diuretic or non-diuretic antihypertensive drugs was established if a subject reported either general use or a specific brand name (7).

At the end of the interview, the respondents were given a standardized, self-administered food-frequency questionnaire (13), which sought usual adult dietary practices prior to 1987, to be completed later and returned by mail. The diet questionnaires were then edited, and items left unanswered or requiring clarification were retrieved in a follow-up telephone call by the interviewer. The questionnaire included the frequency and portion size of 65 food items, selected restaurant foods and fast foods, types of fat usually used, degree of "doneness" and the method of cooking red meat, and the use of supplemental vitamins and minerals (4).

All analyses presented in this paper were based on directly interviewed subjects. Information from next-of-kin cases was examined separately solely to evaluate the consistency of results.

Odds ratios and corresponding 95 percent confidence intervals of renal cell cancer were computed by means of unconditional logistic regression (14). The risk factors under study were smoking status in 1987 (nonsmoker, ex-smoker, current smoker of $\leq$1 pack/day of cigarettes, current smoker of $>$1 pack/day of cigarettes, current non-cigarette smoker); hypertension defined by a report of high blood pressure or use (as defined above) of either diuretics (regardless of indication) or other antihypertensive drugs prior to 1987 (yes, no); BMI at usual adult weight (in quartiles); total protein intake prior to 1987 (in quartiles); history of kidney disease defined as either stone, injury, or infection prior to 1987 (yes, no); and number of births as of 1987 (0, 1–2, 3–4, $\geq$5) for women. It should be noted that previous evidence regarding association of renal cell cancer with the last three risk factors was not as strong as with the first three risk factors. We ran overall analyses (for all study subjects) and sex-specific analyses. All models included the frequency-matching variables, age ($\leq$58, 59–69, $\geq$70) and sex (except for the sex-specific models that could only include age). Furthermore, all models with either smoking, hypertension, or BMI included the other two variables to control for reciprocal confounding. Protein intake was adjusted for BMI, smoking, and total caloric intake (quartiles). Kidney disease was adjusted for smoking, hypertension, and BMI. Number of births was adjusted for smoking and BMI. Finally, quartiles of total caloric intake, protein intake, and BMI were defined separately for men and women for the sex-specific analyses, and from all controls for the overall analyses. For BMI, the definition for men (weight (kg)/ height $(m)^2$) was used to define overall quartiles.

Estimates of population attributable risk (PAR) and corresponding 95 percent confidence intervals were obtained by using an approach based on unconditional logistic regression (15–16). By combining adjusted odds ratio estimates and the observed prevalence of the risk factors under study in the cases, this approach yields adjusted PAR estimates. The same logistic models were used for odds ratio and PAR estimation, thereby allowing adjustment of PAR estimates for the

same factors and in the same manner as for odds ratio estimates. For some risk factors (namely, smoking, BMI, protein intake, and number of births), level-specific PARs were estimated in addition to overall PARs. Overall PARs measure the impact of any exposure to the risk factor, while level-specific PARs measure the impact of a specific level of exposure. PARs were estimated for combinations of risk factors as well as for each separate risk factor. It should be noted that because the logistic model assumes a multiplicative effect on the odds ratio scale, the PAR for the combination of two or more risk factors is usually less than the sum of the PARs for each risk factor.

In order to interpret a PAR as the proportion of cases caused by a risk factor and thus that could be prevented by its elimination from the population, causality needs to be proven. PARs are usually estimated for well-established risk factors whether causality is proven or not. For more speculative risk factors, PAR estimates can be regarded as measuring their potential impact on disease incidence and the potential reduction in disease incidence that could be attained from their elimination were they later proven to be causal. Such an interpretation has been used by several authors (e.g., see references 17–19). We present PAR estimates for both types of risk factors in the results and clearly distinguish between them.

RESULTS

Directly interviewed cases and controls were similar in distribution by sex, age (median and mean ages were 64 and 62 years, respectively, for both cases and controls), and educational level (table 1). For the three main risk factors for renal cell carcinoma under study, PAR estimates are presented in table 2. Estimates of odds ratios and of the prevalence of exposure, both of which influence the PAR estimates, are also shown.

Current smokers had a significant excess risk of about 50 percent, yielding a PAR of 9 percent. The lingering risk of having smoked in ex-smokers (odds ratio (OR) = 1.3) resulted in a PAR resembling that of current smokers (PAR = 8 percent in ex-smokers) due to the high prevalence (39 percent) of past smoking. Overall, the PAR for ever smoking was 18 percent, with the impact being more pronounced among men (PAR = 27 percent) than among women (PAR = 10 percent) mainly because of a higher prevalence of past smoking among men.

Hypertension was associated with a significant excess risk of 70 percent, which, coupled with its relatively high prevalence in Minnesota, resulted in a PAR of 21 percent. The risk was significantly more pronounced ($p = 0.02$) among women than among men. Women also had a slightly higher prevalence of hypertension, so that its impact was much greater among women (PAR = 39 percent) than among men (PAR = 12 percent).

The risk of renal cell cancer increased with BMI, with a significant 60 percent excess risk in the highest quartile compared with the lowest quartile. Overall, 21 percent of cases could be attributed to a BMI level above the lowest quartile, with most of the PAR concentrated in the top quartile. The effect of BMI seemed more pronounced among women than men, although the difference was not significant. Relative to those in the lowest quartile of BMI, the odds ratios for women in the second, third, and fourth quartiles of BMI were 1.3, 2.2, and 2.3, respectively. The corresponding odds

TABLE 1. Sociodemographic characteristics of cases and controls in a case-control study in Minnesota, 1988–1990*

Characteristic	Cases ($n = 690$)		Controls ($n = 707$)	
	No.	%	No.	%
Sex				
Females	171	38	238	34
Males	278	62	469	66
Age (years) at interview				
≤58	162	36	252	36
59–69	156	35	230	33
≥70	131	29	225	32
Education				
Not a high school graduate	108	24	170	25
High/technical school graduate	193	44	285	41
College	141	32	236	34
Interview type				
Direct interview	449	65	707	100
Next-of-kin interview	241	35	0	0

* For all characteristics except interview type, counts refer to directly interviewed subjects only.

TABLE 2. Odds ratios (OR) and population attributable risks (PAR) and 95% confidence intervals (CI) for the three main risk factors of renal cell cancer in a case-control study in Minnesota, 1988–1990

Risk factor	OR	95% CI	Controls with risk factor (%)	All subjects		Men		Women	
				PAR	95% CI	PAR	95% CI	PAR	95% CI
Smoking*									
Nonsmoker	1.0		34.6						
Ex-smoker	1.3	0.9 to 1.7	39.0	8.2	−2.1 to 18.4	12.9	−2.7 to 28.5	5.6	5.1 to 16.3
Current cigarette smoker (≤1 pack/day)	1.5	1.0 to 2.2	14.2	5.1	0.0 to 10.2	7.1	0.8 to 13.3	2.0	−7.0 to 11.1
Current cigarette smoker (>1 pack/day)	1.6	1.0 to 2.7	7.5	3.6	0.0 to 7.3	5.1	−0.2 to 10.3	2.4	−1.6 to 6.3
Current non-cigarette smoker	1.3	0.7 to 2.4	4.8	1.1	−1.6 to 3.9	2.4	−1.8 to 6.6	NA§	
Any tobacco			65.5	18.0	2.6 to 33.4	27.4	4.0 to 50.9	10.0	−6.4 to 26.4
Hypertension†									
No	1.0		60.5						
Yes	1.7	1.3 to 2.2	39.5	21.1	11.4 to 30.7	12.1	0.5 to 23.7	39.3	23.5 to 55.2
Body mass index (BMI) at usual weight, by quartile‡									
1	1.0		25.0						
2	1.1	0.8 to 1.7	24.9	2.9	−4.7 to 10.4	−4.2	−14.4 to 6.0	4.9	−5.9 to 15.8
3	1.3	0.9 to 1.8	25.0	5.4	−2.5 to 13.2	1.8	−8.4 to 12.1	17.3	5.4 to 29.2
4	1.6	1.1 to 2.3	25.0	12.2	3.7 to 20.7	7.2	−4.2 to 18.7	20.7	7.8 to 33.6
2–4			75.0	20.5	1.1 to 39.8	4.9	−21.3 to 31.0	42.9	15.0 to 70.8

* OR and PAR estimates adjusted for usual BMI (quartiles), hypertension (present, absent for the combined variable), age (≤58, 59–69, ≥70 years), and sex (where applicable).

† OR and PAR estimates adjusted for usual BMI (quartiles), smoking (nonsmoker, ex-smoker, current light cigarette smoker, current heavy cigarette smoker, current non-cigarette smoker), age (≤58, 59–69, ≥70 years), and sex (where applicable).

‡ OR and PAR estimates adjusted for smoking (nonsmoker, ex-smoker, current light cigarette smoker, current heavy cigarette smoker, current non-cigarette smoker), hypertension (present, absent for the combined variable), age (≤58, 59–69, ≥70 years), and sex (where applicable).

§ NA, not applicable.

ratios for men were 0.8, 1.1, and 1.3, respectively. Thus, BMI was the risk factor with the greatest impact among women (PAR = 43 percent) with the top quartile alone accounting for 21 percent of the cases, while among men its impact was marginal (PAR = 5 percent).

Among the more speculative risk factors, total protein intake appeared to have the largest potential impact on renal cell cancer, with a PAR of 19 percent (95 percent CI −14 to 52) for any intake above the first quartile. Sex differences were minor. Although kidney disease was associated with a significant excess risk of 40 percent, its prevalence was low, so its impact was minor (PAR = 5 percent overall; 95 percent CI 0–10).

Among women, high parity was associated with an increased risk of renal cell cancer. A twofold risk was estimated for women with ≥5 births compared with nulliparous women. Given the high prevalence of large families in Minnesota (56 percent of control women gave birth to ≥3 children, and 21 percent gave birth to ≥5 children), the PAR for parity was 26 percent (95 percent CI −21 to 74). High parity (number of births ≥3) alone accounted for this high PAR value, and an analysis combining the categories of nulliparity and low parity (number of births ≤2) increased the PAR for high parity to 30 percent (95 percent CI −10 to 70).

In the overall study population, 49 percent of cases could be attributed to at least one of the three well-established risk factors (95 percent CI 32–65). Among men, this proportion was only 39 percent (95 percent CI 13–66) and it rose to 68 percent (95 percent CI 49–87) among women. When total protein intake and kidney disease were also considered, the resulting PAR was 60 percent overall (95 percent CI 39–81), 60 percent in men (95 percent CI 34–87), and 74 percent in women (95 percent CI 51–97), the latter figure rising to 78 percent when parity was also taken into account (95 percent CI 54–102).

DISCUSSION

In a population-based case-control study of renal cell cancer in Minnesota, 49 percent of cases could be attributed to at least one of the three main risk factors, smoking, hypertension, and elevated BMI.

The body of evidence relating these three risk factors with renal cell cancer is extensive. Smoking and renal cell cancer have been consistently linked in case-control studies (20–30) and cohort studies (31, 32). Our estimates of relative risk fall within the range of 1.2 to 2.3 reported in these studies (33). Smoking is the only factor for which PAR estimates have been reported for renal cell cancer in the literature. Our estimate of 27 percent among men is close to the 30–37 percent range found in earlier case-control

studies in Minnesota (21) and Australia (28). For women, our estimate of 10 percent is close to the 14 percent reported in the Australian study (28), but smaller than the 24 percent noted in the earlier Minnesota study (21) because of the lower magnitude of the odds ratio for smoking.

Among women, excess weight has been linked to renal cell cancer in most case-control studies (20–22, 26, 27, 29, 34–41) as well as cohort studies (42–44). Our findings are in line with the reported odds ratio estimates for usual BMI. The impact of BMI among women (PAR = 43 percent) exceeded that of other risk factors, with the most pronounced effect in the heaviest women (PAR = 21 percent in the top quartile). Among men, no consistent association with obesity was observed in early studies (20, 34, 42), but recent studies have found such an association, although less pronounced than among women (21, 22, 26, 27, 29, 35–38, 41, 43). Our results among men fit this pattern, as only the top quartile of BMI showed a slight elevation in risk, resulting in a PAR of only 5 percent. The apparent sex-difference in risk associated with BMI may originate from the associations with BMI being modified by sex-specific variations in metabolism, energy balance, or hormonal status. Such effects have been shown in colon cancer (45). Finally, in our evaluation of preventable risk factors, we felt that usual BMI would be the most clearly interpreted variable. However, odds ratio estimates are given by Chow et al. (8) for various measures of excess weight such as highest or current BMI in our study population, and we computed PAR estimates which were qualitatively similar with these alternative measures (data not shown).

To evaluate hypertension, we used a combined variable that reflected a personal history of hypertension or treatment by either diuretics or non-diuretic antihypertensive drugs. For the purpose of this PAR study, we did not attempt to distinguish among these components, because it remains unclear whether hypertension or its treatment is the important risk factor (7). The elevated relative risk we observed in association with hypertension is consistent with previous studies that have found a link between renal cell cancer and use of diuretics (22, 27, 29, 39, 46–51), use of non-diuretic antihypertensive drugs (37), and a personal history of hypertension irrespective of therapy (27, 37). Given the high prevalence of hypertension in Minnesota, at least by our definition, the PAR for hypertension was high. Moreover, our results suggest a significantly stronger effect in women, so that, in terms of PAR, hypertension is second to obesity as a risk factor for women. This possible sex difference does not appear to have been noted before.

An etiologic link between dietary variables and renal cell carcinoma is tenuous and has not yet been clearly established (21, 22, 24, 26, 27, 29, 47, 52, 53). For this PAR analysis, we looked only at protein intake, the dietary factor for which there appears to be the most evidence of a link with renal cell cancer, either for consumption of meat (21, 26, 27), milk (24, 26), or animal protein (26). Odds ratio estimates for various nutrients in this study are reported by Chow et al. (4). The odds ratio estimates for protein intake show an excess risk even after adjustment for caloric intake. Our PAR estimates suggest that, if a causal link is established, high protein intake may be an important determinant of renal cell cancer.

For renal disease, we again used a combined variable for the purpose of this analysis, since an association with renal cell cancer has been suggested for kidney infection (21), kidney or bladder stones (53) and urologic disease in general (24). Our odds ratio estimates are consistent with previous studies. Given the small excess risk associated with renal disease and its low prevalence, it does not appear to be a major factor in terms of population impact.

In women, the effect of reproductive factors has been examined in only a few studies. No association with parity or gravidity was found in three studies (27, 37, 41). One study, however, reported a more than twofold risk associated with multiple births, although only among women with a history of pregnancy loss (29). Our results suggest an effect of high parity ($\geq$3 births), as described in more detail by Chow et al. (6), although the findings are not conclusive. If confirmed as a risk factor, parity may have a major impact on renal cell cancer risk in places where high parity is relatively common. Further studies are needed to clarify the role of hormonal and other mechanisms that may underlie this association.

Other risk factors for renal cell carcinoma have been suggested, such as analgesics, coffee, alcohol, occupation, radiation, and familial susceptibility (33). We have not presented results on these variables in the present paper because the epidemiologic evidence to date is inconclusive or because no clear relation was found in our study population (e.g., for analgesics, see Chow et al. (5)).

The main strengths of this study are its large sample size and population setting, with the statewide surveillance system providing nearly complete reporting of cases. There is no reason to think that the controls selected were not representative of this well-defined population. However, 34 percent of cases could not be interviewed directly because of the poor survival from renal cell cancer, so the information was provided by a next-of-kin. In this paper, we limited our results to

directly interviewed subjects, although analyses that included next-of-kin case patients provided similar results, both in terms of odds ratio and PAR estimates. The possible exception is BMI, for which odds ratio and PAR estimates from next-of-kin case patients were slightly smaller (PAR estimates for BMI were, respectively, 15 percent and 21 percent depending on whether or not next-of-kin case patients were included). Dietary information was not obtained for about 20 percent of interviewed cases and controls, which prevents us from excluding biased estimates for protein intake. Finally, our PAR estimates apply to the state of Minnesota, and extrapolations to other areas may be valid only for populations with a similar mix of exposures and susceptibility factors. In particular, German and Scandinavian ethnic groups, which are heavily represented in Minnesota, were reported to have an increased risk of renal cell cancer by McLaughlin et al. (21), although this association was not confirmed by Kreiger et al. (29).

In summary, our results show that about 50 percent of cases of renal cell cancer in Minnesota are associated with the three main risk factors (a proportion that would rise to 60 percent if more speculative risk factors were also considered). If these results applied to the rest of the United States, about 15,000 (or, respectively, 18,000) cases could be prevented potentially every year in the United States by various interventions, especially measures aimed at reducing smoking and excess weight. The findings also indicate that at least 40 percent of cases remain unexplained, which underscores the need for further research into the environmental and genetic determinants of this cancer, particularly in view of the steadily rising incidence rates around the world.

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